Remarks

Claims 21 to 69 were pending and were before the Examiner. By this Amendment, applicants have amended claims 21, 29, 34, 35, 38, 39, and 51 to 54 without changing their scope and added new claim 70. Applicants maintain that no new matter has been added by these amendments and therefore respectfully request that the Examiner enter the amendments presented. Amended claims 21 to 70 are now pending and before the Examiner in this application.

The Examiner rejected claims 21 to 24, 30 to 33, and 39 to 69 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to indicate the hydrogen bonded to the imidazoline ring nitrogen.

In response, applicants have amended claims 21 and 39 to indicate the hydrogen which, according to convention in the art, was understood to be present in the compounds of formula (II) although not explicitly indicated. Applicants maintain that such amendments render the Examiner's rejection under 35 U.S.C. § 112, second paragraph, moot. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection.

The Examiner rejected claims 21 to 26, 29, and 47 to 50 under 35 U.S.C. § 103(a) as allegedly unpatentable over Olson *et al.* (U.S. Patent No. 4,287,201).

In response, applicants respectfully traverse the Examiner's obviousness rejection and contend that the rejection is improper.

First, Olson *et al.* is nonanalogous prior art and cannot be relied on for a rejection under 35 U.S.C. § 103(a). *See* M.P.E.P. § 2141.01(a). "In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1445 (Fed. Cir. 1992); M.P.E.P. § 2141.01(a). Olson *et al.* relates to chicken feed compositions and methods of delaying the onset of egg production in chickens; the instant invention is broadly in the pharmaceutical art, in particular, relating to compounds useful as α_{1L} agonists for treating urinary incontinence. Olson *et al.* is manifestly neither "in the field of applicant's endeavor"

or "reasonably pertinent to the particular problem with which the inventor was concerned" and therefore cannot be relied upon for a rejection under 35 U.S.C. § 103(a). Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 103(a) on this basis alone.

Second, even assuming *arguendo* that Olson *et al.* is analogous prior art, applicants submit that the Examiner has not established a *prima facie* case of obviousness against the instant claimed invention. A *prima facie* case of obviousness requires the satisfaction of three criteria: (i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; (ii) there must be a reasonable expectation of success; and (iii) the references when combined must teach or suggest all of the claim limitations. *See* M.P.E.P. § 2143. In particular, the Examiner has not articulated (1) what is the alleged suggestion or motivation in Olson *et al.* or in the knowledge generally available to one of ordinary skill in the art to modify Olson *et al.* in any way to obtain the instant invention, (2) why there would be a reasonable expectation of success for modifying Olson *et al.* to obtain the instant claimed invention, especially given the unrelated and dissimilar subject matter of Olson *et al.*, or (3) how Olson *et al.* can fairly be seen as teaching or suggesting all of the claim limitations of the instant claims.

Accordingly, applicants maintain that this rejection is improper and respectfully request that the Examiner reconsider and withdraw the rejection. Applicants point out that claim 29 has been amended to remove 2-(3-dimethylamino-2-methylphenylimino)imidazolidine, or a pharmaceutically acceptable salt thereof, which the basis for the Examiner's rejection of that claim. This removed subject matter has been claimed in new claim 70.

The Examiner also rejected claims 21 to 24, 30 to 33, 39 to 50, and 55 to 65 under 35 U.S.C. § 103(a) as allegedly unpatentable over York (U.S. Patent No. 4,461,904) or Stahle *et al.* (U.S. Patent No. 4,213,995) or Stahle *et al.* (EP 012822).

In response, applicants respectfully traverse the Examiner's obviousness rejections and contend that the rejections are improper. A *prima facie* case of obviousness requires the satisfaction of three criteria: (i) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the

art, to modify the reference or combine reference teachings; (ii) there must be a reasonable expectation of success; and (iii) the references when combined must teach or suggest all of the claim limitations. *See* M.P.E.P. § 2143.

With regard to York '904, the Examiner has noted Examples V and VI as particularly relevant. Both of these Examples, however, as with all the compounds of York '904, are outside the scope of the claims and differ from applicants' claimed compounds in significant and unobvious ways. For example, Examples V and VI of York '904 have an $R_3 = -NH_2$ group, while applicants' claims 21 and 39 recite a compound of formula (II) where R^2 (the position corresponding to R_3 in York '904) is a substituted amino group or a heterocycle.

With regard to Stahle *et al.* '995, the Examiner has noted Example 5 as particularly relevant. Example 5, however, as with all the compounds of Stahle *et al.* '995, are outside the scope of the claims and differ from applicants' claimed compounds in significant and unobvious ways. For example, Example 5 of Stahle *et al.* '995 does not have a group corresponding to the R^2 = substituted amino group or a heterocycle of applicants' claims 21 and 39.

With regard to Stahle *et al.* EP '822, the Examiner has noted Example 2 as particularly relevant. Example 2, however, as with all the compounds of Stahle *et al.* EP '822, are outside the scope of the claims and differ from applicants' claimed compounds in significant and unobvious ways. For example, Example 2 of Stahle *et al.* EP '822 does not have a group corresponding to the R^2 = substituted amino group or a heterocycle of applicants' claims 21 and 39.

The Examiner has not adequately explained the motivation for modifying the compounds York '904, Stahle *et al.* '995, or Stahle *et al.* EP '822 to obtain applicants' claimed invention. That is, the Examiner has not explained why one of skill in the art would, other then by impermissibly resorting to the teachings of applicants' disclosure:

(1) modify an unsubstituted amino group of Examples V and VI of York '904 to obtain a substituted amino group or a heterocycle at a position corresponding to R^2 of the compound of formula (II) of applicant's claimed invention, or

(2) add a substituted amino group or a heterocycle at a position corresponding to R^2 where only a hydrogen group exists to Example 5 of Stahle *et al.* '995 or Example 2

of Stahle *et al.* EP '822 to obtain the compound of formula (II) of applicant's claimed invention.

The Examiner has provided no rational support for position (2), changing the hydrogen at a position corresponding to R^2 on Example 5 of Stahle *et al.* '995 or Example 2 of Stahle *et al.* EP '822 to a substituted amino group or a heterocycle to obtain the compound of formula (II) of applicant's claimed invention.

In support of position (1), the Examiner has cited *Ex parte Weston*, 121 U.S.P.Q. 428 (P.O.B.A. 1958) and *In re Hoeksema*, 158 U.S.P.Q. 596 (C.C.P.A. 1968) for the broad proposition that "it is obvious to replace a hydrogen with a lower alkyl group on a nitrogen atom" (Office Action, page 5). Neither case supports this unrestricted and broad proposition. For example, *Ex parte Weston* involved an applicant (Weston) who had originally claimed both N-benzhydrylpiperazines that were N-substituted by hydrogen (monosubstituted piperazines) or by C_{1-4} alkyl (disubstituted piperazines). Weston "originally disclosed the hydrogen and methyl substituents on the N' atom of the piperazine to be full equivalents" and therefore because of this admission by Weston could not successfully now argue that the monosubstituted piperazines were not obvious over the disubstituted piperazines. *Ex parte Weston*, 121 U.S.P.Q. 428, 429. Applicants have made no such admission, so *Ex parte Weston* is irrelevant to the instant situation. Similarly, *In re Hoeksema*, involved a situation where the applicant (Hoeksema) successfully removed a reference as prior art by submitting an affidavit that the alleged prior art did not disclose a way to make the disclosed compounds in the reference and the reference did not therefore put the invention in the possession of the public. Hoeksema conceded that his compounds would have been obvious over the reference, so the issue of obviousness was admitted, not proven (the earlier case *In re Hoeksema*, 154 U.S.P.Q. 169, 172 (C.C.P.A. 1967) makes this clear). Thus, both *Ex parte Weston* and *In re Hoeksema*, 158 U.S.P.Q. 596 (C.C.P.A. 1968), should properly be limited to situations where the applicant admits or concedes that a particular amino substitution is equivalent to or obvious over another amino substitution: such is not the situation here.

The Examiner seems to be improperly focusing on the obviousness of the differences between the claimed invention and the prior art rather than on the obviousness of the claimed invention as a whole as § 103 requires. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986)(emphasis added). Obviousness cannot be established by

hindsight combination to produce the claimed invention or in view of the teachings or suggestions of the inventor. *In re Dance*, 48 U.S.P.Q.2d 1635 (Fed. Cir. 1998); *In re Gorman*, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991). Examiners must state clearly and specifically any objections to patentability to establish the elements of a *prima facie* case and give the applicant fair opportunity to meet those objections with evidence and argument. *In re Oetiker*, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992)(Plager, J., concurring).

Furthermore, characterization of a claimed compound as "similar" or "slightly different" from compounds taught in the prior art does not establish the obviousness of the use of compound that is new and nonobvious, since the mere chemical possibility that a prior art compound could be modified does not support a finding of obviousness unless the prior art suggested the desirability of such a modification. *In re Ochiai*, 37 U.S.P.Q.2d 1127 (Fed. Cir. 1995); see also *In re Gordon*, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) *In re Bergel*, 130 U.S.P.Q. 206, 208 (C.C.P.A. 1961). Similarity is not necessarily obviousness. *In re Ochiai*, 37 U.S.P.Q.2d 1127 (Fed. Cir. 1995); *In re Grabiak*, 226 U.S.P.Q. 870 (Fed. Cir. 1985)(substitution of thioester for ester functionality not obvious). The necessary changes or modifications in the prior art to obtain the claimed invention must be evaluated in terms of the whole invention, including whether the prior art provides any teaching or suggestion to one of ordinary skill in the art to make the changes that would produce the applicant's invention, regardless of whether the changes from the prior art are considered "minor". *In re Chu*, 36 U.S.P.Q.2d 1089 (Fed. Cir. 1995); *Northern Telecom, Inc. v. Datapoint Corp.*, 15 U.S.P.Q.2d 1321, 1324 (Fed. Cir.), *cert. denied*, 498 U.S. 920 (1990); *In re Gordon*, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984).

Accordingly, there is no need to submit evidence of unobvious or unexpected results. Where a *prima facie* case of obviousness has not been established there is no need for comparative tests or a showing of "unexpected results", since there is no rejection that must be overcome. *In re Benno*, 226 U.S.P.Q. 683 (Fed. Cir. 1985).

The Examiner objected to claims 34 to 38 and 51 to 54 as being dependent on a rejected base claim but concluded that they would be allowable if rewritten in independent form.

In response, applicants respectfully traverse the objection. Claims 36 and 37 are dependent from allowed claims 27 and 28. Furthermore, claims 34, 35, 38, and 51 to 54 have been

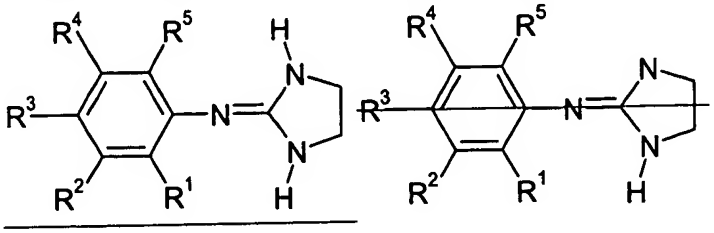
amended to put them in independent form. Therefore, applicants respectfully request that the Examiner reconsider and withdraw this objection.

Applicants thank the Examiner for allowing claims 27 and 28. Applicants, however, submit that all the pending claims are allowable and respectfully solicit a Notice of Allowance for all of the pending claims. If the Examiner feels that a telephone interview would be helpful in advancing prosecution of this application, the Examiner is invited to contact the attorney below.

Version of the Claims with Markings to Show Changes Made by this Amendment

In accordance with 37 C.F.R. § 1.121(c)(1)(ii), the following marked up version of the claims amended herein is provided to show all of the changes relative to the previous version of the claims before the amendments herein.

--21. (Four times amended) A compound of the formula (II)



(II)

wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{3-6}-cycloalkyl, C_{1-6}-alkoxy, halogen, $-CF_3$, or $-OCF_3$;

R^2 is $-NR^6R^7$, wherein

R^6 is methyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, or C_{3-6}-cycloalkyl,

R^7 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{3-6}-cycloalkyl, or C_{2-4}-acyl, or

R^6 and R^7 together with the nitrogen between them form a 5- or 6-membered, saturated or unsaturated ring containing 0, 1, or 2 additional heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, wherein each additional nitrogen atom is unsubstituted or substituted by methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl, or R^6 and R^7 together with the nitrogen between them form phthalimido;

R^3 is hydrogen, halogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{1-6}-alkoxy, $-CF_3$, or $-OCF_3$;

R^4 is hydrogen, halogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, or hexyl; and

R^5 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{1-6}-alkoxy, halogen, $-CF_3$, or $-OCF_3$;

or a pharmaceutically acceptable salt thereof.--

--29. (Amended) A compound selected from the group consisting of:

~~(a) 2-(3-dimethylamino-2-methylphenylimino)imidazolidine,~~

(~~b~~a) 2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,

(e~~b~~) 2-(2-methyl-3-phthalimidophenylimino)imidazolidine,

(~~d~~c) 2-(3-acetylamino-6-chlorophenylimino)imidazolidine,

(ed) 2-(3-amino-2-methylphenylimino)imidazolidine,

(~~f~~e) 2-(3-amino-4,6-dibromo-2-methylphenylimino)imidazolidine,

(gf) 2-(3-amino-4-methylphenylimino)imidazolidine,

(~~h~~g) 2-(4,6-dibromo-3-dimethylamino-2-methylphenylimino)imidazolidine,

(~~i~~h) 2-(4-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,

(~~j~~i) 2-(6-chloro-3-dimethylamino-2-methylphenylimino)imidazolidine, and

(~~k~~j) 2-(6-chloro-3-phthalimidophenylimino)imidazolidine,

or a pharmaceutically acceptable salt thereof.--

--34. (Amended) A pharmaceutical composition comprising:

(a) a compound ~~in accordance with claim 25~~selected from the group consisting of:

2-(3-dimethylamino-2-methylphenylimino)imidazolidine,

2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,

2-(5-amino-2-chloro-4-dimethylamino-2-methylphenylimino)imidazolidine, and

2-(3-amino-2-methylphenylimino)imidazolidine,

or a pharmaceutically acceptable salt thereof, and

(b) one or more pharmaceutically acceptable excipients, adjuvants, carriers, or preservatives.--

--35. (Amended) A pharmaceutical composition comprising ~~a compound in accordance with claim 26~~2-(3-dimethylamino-2-methylphenylimino)imidazolidine, or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients, adjuvants, carriers, or preservatives.--

--38. (Amended) A pharmaceutical composition comprising:

(a) a compound ~~in accordance with claim 29~~selected from the group consisting of:

2-(3-dimethylamino-2-methylphenylimino)imidazolidine,

2-(6-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,

2-(2-methyl-3-phthalimidophenylimino)imidazolidine,

2-(3-acetylamino-6-chlorophenylimino)imidazolidine,

2-(3-amino-2-methylphenylimino)imidazolidine,

2-(3-amino-4,6-dibromo-2-methylphenylimino)imidazolidine,

2-(3-amino-4-methylphenylimino)imidazolidine,

2-(4,6-dibromo-3-dimethylamino-2-methylphenylimino)imidazolidine,

2-(4-bromo-3-dimethylamino-2-methylphenylimino)imidazolidine,

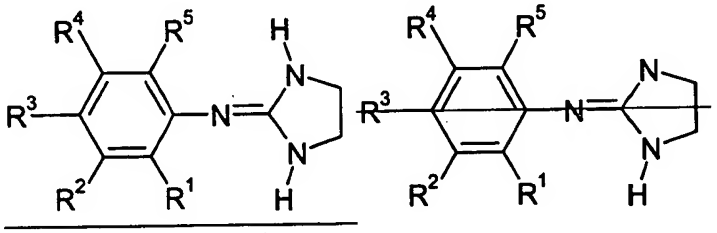
2-(6-chloro-3-dimethylamino-2-methylphenylimino)imidazolidine,

2-(6-chloro-3-phthalimidophenylimino)imidazolidine,

or a pharmaceutically acceptable salt thereof;~~,~~ and

(b) one or more pharmaceutically acceptable excipients, adjuvants, carriers, or preservatives.--

--39. (Twice amended) A pharmaceutical composition comprising a compound of the formula (II)



(II)

wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{3-6}-cycloalkyl, C_{1-6}-alkoxy, halogen, $-CF_3$, or $-OCF_3$;

R^2 is $-NR^6R^7$, wherein

R^6 is ethyl,

R^7 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{3-6}-cycloalkyl, or C_{2-4}-acyl, or

R^6 and R^7 together with the nitrogen between them form a 5- or 6-membered, saturated or unsaturated ring containing 0, 1, or 2 additional heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, wherein each additional nitrogen atom is unsubstituted or substituted by methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl, or R^6 and R^7 together with the nitrogen between them form phthalimido;

R^3 is hydrogen, halogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{1-6}-alkoxy, $-CF_3$, or $-OCF_3$;

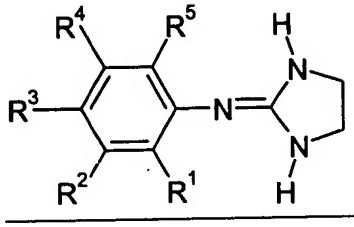
R^4 is hydrogen, halogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, or hexyl; and

R^5 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{1-6}-alkoxy, halogen, $-CF_3$, or $-OCF_3$;

or a pharmaceutically acceptable salt thereof; and

one or more pharmaceutically acceptable excipients, adjuvants, carriers, or preservatives.--

--51. (Amended) ~~The~~A compound of the formula (II) ~~according to claim 21~~



(II)

wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{3-6}-cycloalkyl, C_{1-6}-alkoxy, halogen, $-CF_3$, or $-OCF_3$;

R^2 is $-NR^6R^7$, wherein R^6 and R^7 together with the nitrogen between them form a 5- or 6-membered, saturated or unsaturated ring containing 0, 1, or 2 additional heteroatoms selected from the group consisting of oxygen, sulfur, and nitrogen, wherein each additional nitrogen atom is unsubstituted or substituted by methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or *tert*-butyl, or R^6 and R^7 together with the nitrogen between them form phthalimido;

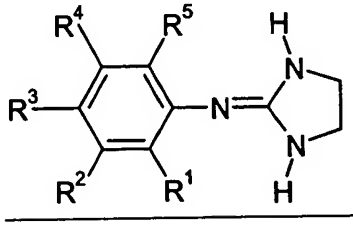
R^3 is hydrogen, halogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{1-6}-alkoxy, $-CF_3$, or $-OCF_3$;

R^4 is hydrogen, halogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, or hexyl; and

R^5 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, C_{1-6}-alkoxy, halogen, $-CF_3$, or $-OCF_3$;

or a pharmaceutically acceptable salt thereof.--

--52. (Amended) ~~The~~A compound of the formula (II) ~~according to claim 22,~~



(II)

wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, cyclopropyl, C_{1-4}-alkoxy, halogen, $-CF_3$, or $-OCF_3$;

R^2 is $-NR^6R^7$, wherein R^6 and R^7 together with the nitrogen between them form phthalimido;

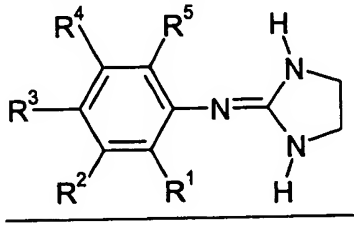
R^3 is hydrogen, halogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, C_{1-4}-alkoxy, $-CF_3$, or $-OCF_3$;

R^4 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, or halogen; and,

R^5 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, C_{1-4}-alkoxy, halogen, $-CF_3$, or $-OCF_3$;

or a pharmaceutically acceptable salt thereof.--

--53. (Amended) ~~The~~A compound of the formula (II)~~ according to claim 23,~~



(II)

wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, cyclopropyl, C_{1-3}-alkoxy, halogen, or $-CF_3$;

R^2 is $-NR^6R^7$, wherein R^6 and R^7 together with the nitrogen between them form phthalimido;

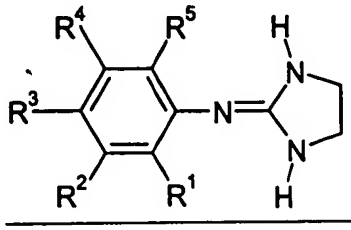
R^3 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, C_{1-3}-alkoxy, halogen, or $-CF_3$;

R^4 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, or halogen; and,

R^5 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, C_{1-3}-alkoxy, halogen, or $-CF_3$;

or a pharmaceutically acceptable salt thereof.--

--54. (Amended) ~~The~~A compound of the formula (II)~~ according to claim 24,~~



(II)

wherein:

R^1 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, or halogen;

R^2 is $-NR^6R^7$, wherein R^6 and R^7 together with the nitrogen between them form phthalimido;

R^3 is hydrogen, methyl, fluorine, chlorine, or bromine;

R^4 is hydrogen; and

R^5 is hydrogen, methyl, chlorine, or bromine;

or a pharmaceutically acceptable salt thereof.--

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Timothy Witkowski

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7-17-2002
Dated

Respectfully submitted,

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